DETAILED ACTION

Applicant's argument filed, in the paper 12/1/2008, is acknowledged. Claims 15 and 21-28 are still at issue and are present for examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15 and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gelfand et al. (US 6,346,379) and Gelfand et al. (US 6,228,628 B1).

The rejection was stated in the previous office action as it applies to claims 15 and 23-28. In response to this rejection applicants have not amended the claims, but merely argue the rejection.

Applicants traverse the rejection on the basis that Applicants submit that the Gelfand '379 patent does not teach an E681R mutation, but rather it reports a Taq polymerase with the E681K (lysine) mutation. Applicants submit that further, while the patent stresses the importance of the 681 position what it actually says is "changes in the structure of the O a-O b helix other than E to K at position 681 are also expected to produce changes in the ability of the polymerase to discriminate against nucleotides labeled with fluorescein family dyes". Thus, they teach that some change may be expected without knowing the nature of this change except for the single mutation they studied, E681K.

In response to applicant's assertion, Gelfand et al. '379 do teach an E681R mutation at column 8, line 36-38, referring to position 681, Gelfand et al. teach:

"...In a more preferred embodiment, the X at position 4 is replaced by an amino acid having a positive charge, such as K, R or H, or by a polar amino acid such as Q or N. In a most preferred embodiment, the X at position 4 is replaced by K...."

Thus applicant's assertion that Gelfand '379 does not teach an E681R mutation is not found persuasive.

As previously stated, one of skill in the art at the time of filing would have been motivated to recombinantly make a mutant Taq DNA polymerase comprising a F667Y mutation and a E681R mutation, as taught by Gelfand et al., and a D18A mutation as taught by Gelfand et al. This mutant Taq DNA polymerase would inherently comprise the amino acid sequence set forth in Figure 3 or SEQ ID NO:3. The motivation for the creation of this triple mutant is that the F667Y mutation and E681R mutations taught by Gelfand et al. (US 6,346,379) are each in the region identified by Gelfand et al. as critical to the incorporation of fluorescein family dyes and the mutation, D18A, taught by Gelfand et al. is in a region critical in the 5'-nuclease activity, both related activities.

Applicants further submit that the present invention discloses a series of mutations including E681R, E681M, E681H and E681W and these 4 variants, and the wild-type E681 have differing behaviors in critical applications such as DNA sequencing. Thus demonstrating that both the position of the amino acid change (681) and the particular amino acid substituted for E681 are important for activity. While this is acknowledged and would be generally appreciated by one of skill in the art, applicants are reminded that Gelfand '379 teach that the specific mutations at position 681 is not

as critical as is the position (i.e. position 681) that is mutated with regard to the incorporation fluorescein family of dyes, thus certainly adding to the teaching of a mutation at the position 681 from E to R.

Applicants submit that furthermore, the Gelfand '379 patent reports discrimination against nucleotides labeled with "fluorescein family dyes" which are described as including FAM, HEX, TET, JOE, NAN and ZOE. Applicants submit that their examples however are limited to an undefined dye "ZOWIE" which is attached to ddCTP in an undisclosed structure and this is in contrast to the Examples of the current application which were conducted with a number of different dye-labeled nucleotides, including those tagged with rhodamine dyes ROX, R110, R6G and TAMRA (using the nomenclature of Gelfand et al. '379). Applicants statement here is recognized, however, it is unclear as to how this statement or applicants submission of specific examples of the Gelfand '379 patent relate to the rejection at hand. Clarification to this point would be appreciated. If it is applicant's intent to suggest that the Gelfand et al. '379 patent is not enabled, for these specific teachings, this is not found persuasive, as the Gelfand et al. '379 patent is considered enabled sufficient to make obvious the rejected claims, which do not require a specific fluorescent dye labeled nucleotide.

Thus applicant's conclusion that Gelfand et al. (US 6,228,628) does not disclose or suggest the desirability of an E681R mutation and thus a Taq polymerase with a triple mutation of D18A, F667Y, and E681R is not found persuasive.

As previously stated, Gelfand et al. (US 6,346,379) teach a mutant thermostable Taq polymerase comprising a F667Y mutation and an E681R mutation, wherein said thermostable DNA polymerase has reduced discrimination against incorporation of nucleotides labeled with fluorescein family dyes in comparison to the native form of said enzyme. Gelfand et al. teach that while the specific mutations at position 681 is not as critical as is the position (i.e. position 681) that is mutated. Gelfand et al. also teach methods of synthesizing fluorescently labeled polynucleotides comprising the use of said mutated Taq DNA polymerase as well as kits comprising said mutant Taq DNA polymerase.

Gelfand et al. (US 6,228,628 B1) teach mutant Taq DNA polymerases comprising a D18A mutation, wherein said mutant DNA polymerase has a reduced 5' nuclease activity and the use of these mutant DNA polymerases in methods of sequencing using fluorescent dye-terminators and kits comprising said Taq polymerase mutants.

One of skill in the art at the time of filing would have been motivated to recombinantly make a mutant Taq DNA polymerase comprising a F667Y mutation and a E681R mutation, as taught by Gelfand et al., and a D18A mutation as taught by Gelfand et al. This mutant Taq DNA polymerase would inherently comprise the amino acid sequence set forth in Figure 3 or SEQ IDNO:3. The motivation for the creation of this triple mutant is that the F667Y mutation and E681R mutations taught by Gelfand et al. (US 6,346,379) are each in the region identified by Gelfand et al. as critical to the incorporation of fluorescein family dyes and the mutation, D18A, taught by Gelfand et al.

is in a region critical in the 5'-nuclease activity. Each of the different groups of mutations are shown to result in the same functional change, critical to the incorporation of fluorscein dyes, while they each occur at opposite ends of the polymerase molecule. Thus one of skill in the art would have been motivated to combine these mutants at opposite ends of the polymerase molecule because based on there position in the molecule the effect of the combined mutant would likely be cumulative. The expectation of success is high based upon the results of both Gelfand et al. patents that show that such mutants can easily be made including double and triple mutants and the creation of such would lead to predictable results. Thus claims 15 and 23-28 are obvious over Gelfand et al. (US 6,346,379) rangeland et al. (US 6,228,628 B1).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rgh
2/25/2009

/Richard G Hutson/
Primary Examiner, Art Unit 1652